**AMENDMENTS TO THE CLAIMS:**

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Currently Amended) A method for ~~preventing or~~ treating ~~at least one symptom of~~ a patient suffering from or susceptible to hypercalcemic crisis associated with impaired consciousness, comprising

~~the step of~~ administering to a patient ~~at least one substance~~ a humanized anti-PHTrP antibody capable of inhibiting the binding between PTHrP and a receptor thereof;

allowing the antibody to inhibit the binding of PTHrP to a receptor thereof;

decreasing a blood calcium level by at least 1 mg/dL within 24 hours to effectively treat the patient; and

maintaining the at least 1 mg/dL decrease in blood calcium level over at least 24 hours.

2-3. (Canceled).

4. (Currently Amended) The method according to claim 1, wherein the ~~substance is at least one of a fragment of an~~ humanized anti-PTHrP antibody ~~or a modified form of the fragment~~ is an antibody fragment capable of inhibiting the binding between PTHrP and a receptor thereof.

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5. (Canceled).

6. (Currently Amended) The m~~M~~ethod according to claim 1~~5~~, wherein the humanized antibody is humanized #23-57-137-1 antibody.

7. (Currently Amended) The method according to claim 1~~3~~ or 4, wherein the antibody is a monoclonal antibody.

8. (Previously Presented) The method according to claim 1, wherein the hypercalcemic crisis is hypercalcemic crisis associated with malignant tumor.

9. (New) The method according to claim 1, wherein the hypercalcemic crisis is associated with at least one of coma or cardiac arrest.

10. (New) The method according to claim 1 or 4, wherein the antibody is bound to a carrier.

11. (New) The method according to claim 10, wherein the carrier is PEG.

12. (New) The method according to claim 4, wherein the fragment is chosen from at least one of Fab, scFv, F(ab')2, and Fv.

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13. (New) A method for treating a patient suffering from or susceptible to hypercalcemic crisis associated with impaired consciousness, comprising

administering to a patient a humanized anti-PHTrP antibody inhibiting the binding between PTHrP and a receptor thereof;

allowing the antibody to inhibit the binding of PTHrP and a receptor thereof;

decreasing a blood calcium level to at least 15.0 mg/dl to effectively treat the patient.

14. (New) The method according to claim 13, wherein the patient is administered at least one fragment of the humanized anti-PTHrP antibody.

15. (New) The method according to claim 14, wherein the fragment is chosen from at least one of Fab, scFv, F(ab')2, and Fv.

16. (New) The method according to claim 13, wherein the humanized antibody is humanized #23-57-137-1 antibody.

17. (New) The method according to claim 13 or 14, wherein the antibody is a monoclonal antibody.

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18. (New) The method according to claim 13, wherein the hypercalcemic crisis is hypercalcemic crisis associated with malignant tumor.

19. (New) The method according to claim 13, wherein the hypercalcemic crisis is associated with at least one of coma or cardiac arrest.

20. (New) The method according to claim 13 or 14, wherein the antibody is bound to a carrier.

21. (New) The method according to claim 20, wherein the carrier is PEG.

22. (New) A method for treating a patient suffering from or susceptible to drug-resistant hypercalcemic crisis associated with impaired consciousness, comprising

administering to a patient a humanized anti-PHTrP antibody inhibiting the binding between PTHrP and a receptor thereof;

allowing the antibody to inhibit the binding of PTHrP and a receptor thereof;

decreasing a blood calcium level to effectively treat the patient.

23. (New) The method according to claim 22, wherein the drug-resistant hypercalcemic crisis is defined as a blood calcium level that does not normalize after 24 hours of treatment and remain normal over at least 24 hours with one of the therapeutic

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agents chosen from biphosphonate, calcitonin, a steroid, phosphate buffer, physiological saline, and furosemide.

24. (New) The method according to claim 23, wherein the normal blood calcium level is less than 12 mg/dl.

25. (New) The method according to claim 22, wherein the patient is administered at least one fragment of the humanized anti-PTHrP antibody.

26. (New) The method according to claim 25, wherein the fragment is chosen from at least one of Fab, scFv, F(ab')2, and Fv.

27. (New) The method according to claim 22, wherein the humanized antibody is humanized #23-57-137-1 antibody.

28. (New) The method according to claim 22 or 25, wherein the antibody is a monoclonal antibody.

29. (New) The method according to claim 22, wherein the hypercalcemic crisis is hypercalcemic crisis associated with malignant tumor.

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30. (New) The method according to claim 22, wherein the hypercalcemic crisis is associated with at least one of coma or cardiac arrest.

31. (New) The method according to claim 22 or 25, wherein the antibody is bound to a carrier.

32. (New) The method according to claim 31, wherein the carrier is PEG.

33. (New) The method according to claim 2, wherein the blood calcium level is decreased by at least 2 mg/dL.

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3427, Internal Medicine, 1081-1084, Asakura Shoten, left column, lines 9-11. Applicants have also added new independent claim 13, which contains the phrase "decreasing a blood calcium level to at least 15.0 mg/dl to effectively treat the patient" to further distinguish between the two conditions. This claim is supported in the application by the incorporation by reference of the Harrison reference in the specification. Third, as discussed more in-depth below, current treatments for hypercalcemia are not efficacious in treating hypercalcemic crisis. Thus, the prior art does not teach the presently claimed method.

Additionally, none of these three references describe a specific humanized antibody. Applicants' invention is directed to humanized antibodies and Applicants have amended claim 1 to clarify this aspect of the invention. Applicants have cancelled claims 2, 3, and 5, as they would have been duplicative of amended claim 1. It is widely recognized that it is extremely difficult to produce a humanized antibody that retains the binding properties and functional activity of an original murine or chimeric antibody. Thus, the mere mention of humanizing antibodies in Yoneda et al. is not sufficient to enable the preparation of humanized antibodies and is therefore not anticipating.

**Obviousness Rejection**

The Examiner maintained the rejection of claims 1-8, under 35 U.S.C. § 103(a), as allegedly being obvious over Sato et al. (Journal of Bone and Mineral Research, 8/7:849-60 (1993)) in view of Yoneda et al. (U.S. Patent 5,626,845).

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The Examiner did not find Applicants previous arguments regarding the difference between hypercalcemia and hypercalcemic crisis convincing. The Examiner stated that "both conditions share at least one symptom that is expected to be ameliorated upon administering the substance to a patient." Office Action at page 10.

First, Applicants wish to emphasize the differences between hypercalcemia and hypercalcemic crisis. The main differences between the two conditions are the very rapid rise in calcium levels in hypercalcemic crisis and the more serious symptomology that accompanies the high levels of blood calcium, especially impaired consciousness. Applicants have amended the claims, as discussed above, to reflect these differences.

Further, Applicants note the failure of typical hypercalcemia treatments to treat hypercalcemic crisis. As stated in the specification:

> [C]alcitonin, a steroid, a biphosphonate, phosphate buffer, physiological saline, furosemide or the like is administered to improve hypercalcemia in general conditions. However, these drugs have such disadvantages that therapeutic effects may be depressed when successively administered, that severe adverse side effects may be produced, and that the development of pharmacological effect may be delayed.

Specification, page 3, lines 13-23. Thus, not only are these medications unable to reduce the calcium level because of a loss of efficacy after repeat administration, they also produce severe side effects.

The lack of efficacy of typical hypercalcemia treatments is demonstrated in Figure 5. Calcium levels in a rat model of hypercalcemic crisis are basically unchanged in rats treated with Elcitonin (a calcitonin preparation) and untreated rats after 24 hours. Humanized antibody #23-57-137-1 of the invention, however, is able to reduce blood

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calcium level by 1 mmol/L after 24 hours of treatment. Further, as demonstrated by Figure 6, humanized antibody #23-57-137-1 of the invention is able to increase body weight, whereas elicitonin and control are ineffective. Applicants have added new independent claim 22, and dependent claims thereon, to reflect the ability of the antibody of the invention to treat hypercalcemic crisis, which typical treatments for hypercalcemia have been unable to effectively treat.

Finally, Applicants address the Examiner's argument that "both conditions share at least one symptom that is expected to be ameliorated upon administering the substance to a patient." Applicants have deleted the phrase "at least one symptom of" from claim 1 and listed the various symptoms associated only with hypercalcemic crisis (not simple hypercalcemia) to be treated by the present invention in claim 9. Applicants assert that this obviates the Examiner's rejection of claim 1 and the other claims that are dependent on claim 1.

**Conclusion**

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: September 16, 2003

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